

REMARKS/ARGUMENTS

Application Status

Claims 1-6 and 8-20 are pending in the subject application. Claim 1 has been amended to include culture times of the stem cells prior to adding the test agents and the time for harvesting the cells to determine any tissue specific differentiation. Claim 8 has been amended to include the carbon dioxide conditions. Claims 14, 16 and 17 have been amended to reflect the correct dependency on claim 1, namely the dependency on step (F). No new matter has been added by virtue of these amendments and their entry is respectfully requested.

Rejections Under U.S.C. §103

Claims 1 and 14-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WIPO document No.: 99/10535 to Liu, filed 21 August 1997, published 4 March 1999.

Applicants respectfully traverse.

Applicants invention, is directed in part to agent-induced gene changes of stem cells that are expressed in a tissue-specific manner. Applicants have amended claim 1 to include the number of days in which to culture the cells prior to addition of the agent and the length of time that the cells remain in culture after addition of the agent. Support for the amendment is found throughout the specification and a schematic illustration of the method is shown in figures 1 and 2. The stem cells disclosed by applicants are not committed to, nor predisposed to, any specific cell lineage. (See, for example page 3, lines 7-8. Emphasis added). Regarding the steps disclosed by applicants in claim 1, applicants teach the steps of culturing of embryonic stem cells (*i.e.*, totipotent stem cells) followed by sub-culturing of the stem cells prior to the addition of any agent. Thus, applicants do not merely isolate stem cells and culture but culture the cells in media lacking any factor that may induce differentiation.

In contrast to applicants' invention, Liu '535 does not teach any time frame for culturing cells prior to adding a test agent, nor the amount of time needed to culture stem cells in the presence of a test agent. It is not obvious from one of ordinary skill in the art to determine from

Liu *et al.*, whether stem cells would have to be isolated and cultured for any period of time prior to addition of an agent and for how long they should be cultured in the presence of an agent in order to determine tissue specific differentiation. Undue experimentation would be required under Liu *et al.* to teach what applicants teach. It is also not obvious from Liu *et al.*, whether totipotent stem cells vs. hematopoietic stem cells would need to be cultured over any specific time periods prior to addition of and during addition of an agent. unknown from the reading of Liu whether any totipotent stem cell could even be manipulated to differentiate from a totipotent stem cell to a pluripotent stem cell to a pre-committed stem cell, such as a hematopoietic stem cell.

Regarding the Examiner's allegations that "in view of Liu, one of ordinary skill in the art at the time of invention by Applicant ... would have been motivated to identify drug candidates for promoting tissue-specific differentiation of a stem cell by providing a number of test substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually, under conditions that allow for such differentiation, and analyzing the cells in cultures for increased tissue-specific gene expression markers." Applicants respectfully traverse.

Applicants' claim 1 is directed in part to "at least a first test substance and a second test substance, the first and second test substances having different molecular structures." These first and second test substances with different molecular structures are then administered to stem cells that are first sub-cultured, as discussed above, at least three days prior to exposing each sub-culture to the first and second test substances of different molecular structures. Furthermore, the Examiner admits that "Liu does not teach the aspects of culturing cells" (see page 7, 1st paragraph of the Office Action dated 4/08/2004).

The Examiner alleges that "[i]n view of Liu and Moore, it would have been obvious to modify the teachings of Liu by culturing cells in microtiter plates, at 37 degrees centigrade, with 7.5% carbon dioxide, and for 3 to 21 days, as taught by Moore." Applicants respectfully traverse.

As the Examiner has pointed out, "Moore teaches culture media for establishing growing and maintaining mammalian cells in culture." However, Moore is deficient as it does not teach or disclose how to culture and maintain stem cells. Cells disclosed by Moore are malignant and normal cells. (See Example 2). As one of ordinary skill in the art is aware, cells of different types require different media and growth conditions, such as culturing time frames. The Examiner is basing the culture of all mammalian cells as "taught by Moore." Moore does not teach how to culture all mammalian cells, for example, cells like Schwann cells. Moore also does not teach how to culture stem cells by maintaining them in culture in an undifferentiated state until the addition of a tissue specific differentiation agent is added to the culture. Applicants submit that Moore provides absolutely no guidance as to the culturing and maintenance of stem cells and cannot make up for the deficiencies of Liu. Accordingly, Liu, in view of Moore, would not provide a reasonable expectation of success and nor would a person of ordinary skill in the art be motivated to combine these two references as Moore's teachings do not extend to all mammalian cells including stem cells.

It is respectfully submitted that for the foregoing reasons, claims 1 and 14-19 are patentable over the cited references and satisfy the requirements of 35 U.S.C. § 103(a). As such, these claims are allowable.

Rejection under 35 U.S.C. § 103 (a)

Claims 1-5 and 10-12 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Liu as applied to claim 1 above, and further in view of U.S. Patent No.: 5,874,301 to Keller, of record.

Applicants respectfully traverse.

Applicant's have discussed the instant application as it relates to Liu '535 above, and for the sake of brevity, will not be repeated here as the Examiner raises the same issues on page 8 and 9 of the Office Action. Specifically, Liu '535 does not teach any time frame regarding the contacting of stem cells, especially embryonic stem cells, with a test substance.

Applicants have amended claim 1 to make explicit that which is implicit, namely use of naïve embryonic stem cells. Support for this amendment is found throughout the specification. (See, for example, page 2, lines 13-14, figures 1 and 2 and the Examples which follow). Keller does not teach, either directly or indirectly the subject matter of the instant application. Example 1, cited by the Examiner, teaches the maintenance of an embryonic stem cell cell-line that was originally derived from a mouse strain. (See Keller '301, Example 1, col. 32, lines 30-31). Furthermore, col. 2, lines 5-8 directed to a cell-line that is "referred to as embryonic stem (ES) cells." Therefore, ES cells disclosed by Keller are embryonic stem cell-lines and not naïve, freshly isolated embryonic stem cells as disclosed and taught by applicants. Keller, cannot make up for the deficiencies of Liu *et al.*

It is respectfully submitted that for the foregoing reasons, claims 1-5 and 10-12 are patentable over the cited reference(s) and satisfy the requirements of 35 U.S.C. § 103 (a). As such, these claims are allowable.

Claims 1 and 6 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Liu '535 as applied to claim 1 above, and further in view of Thomson, et al. (1998) Science, 282: 1145-1147, of record.

Applicants respectfully traverse.

Applicants have discussed in detail above, as to why the instant invention is novel and patentable over Liu '535 and for the sake of brevity these arguments will not be repeated here. The Examiner alleges that one of ordinary skill in the art "would have been motivated to modify the teachings of Liu '535 by the use of human embryonic stem cells as taught in Thomson '98, because Thomson '98 teaches that such embryonic stem cells are useful for drug discovery (ABSTRACT)." However, these cells express embryonal carcinoma antigens and stage specific embryonic antigens. See page 1145, col. 3 and figure 3. Thomson '98 also is silent as to when a tissue specific agent should be added to a stem cell culture and for how long and the culturing conditions needed. Accordingly, Liu in view of Thomson '98 does not render the instant invention obvious.

It is respectfully submitted that for the foregoing reasons, claims 1 and 6 are patentable over the cited reference(s) and satisfy the requirements of 35 U.S.C. § 103 (a). As such, these claims are allowable.

Claims 1 and 20 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Liu, as applied to claim 1 above and further in view of U.S. Patent No. 5,143,854 to Pirrung of record.

Applicants respectfully traverse.

Applicants have discussed the novelty of applicants invention over Liu '535 above, and for the sake of brevity, these arguments will not be discussed here.

The Examiner alleges on page 13, 3rd paragraph of the Office Action that: "Pirrung '854 teaches the use of such gene chip technology for the analysis of arrays of peptides for activity (ABSTRACT). Specifically, Pirrung '854 teaches that such technology is useful for '[s]creening large numbers of polymers for biological activity,' (col. 3, lines 39-41)." Applicants respectfully traverse. Pirrung is specifically directed to screening of polypeptides and their binding sites. No where does Pirrung suggest, teach or make obvious in any way how to when and how to culture cells, determine which RNA species are present and how one of ordinary skill in the art could adapt an RNA molecule for use on a chip. Applicants submit that if it were obvious to combine the references, it begs the question as to why, Liu '535 does not teach or disclose gene chip technology since Pirrung '854 issued seven years prior to Liu's filing date, would not have been obvious to Liu? Accordingly, applicants submit that it was not even obvious to Lui '535 to incorporate any disclosure by Pirrung.

It is respectfully submitted that for the foregoing reasons, claims 1 and 20 are patentable over the cited reference(s) and satisfy the requirements of 35 U.S.C. § 103 (a). As such, these claims are allowable.


CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1-6 and 8-20 is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at telephone number shown below.

This response is accompanied by a petition for a two month retroactive extension of time and the required fee. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for a one month retroactive extension of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
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